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***JACC* STATE-OF-THE-ART REVIEW**

Obesity and Acute Pulmonary Embolism

Clinical Implications and Knowledge Gaps

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ABSTRACT

Obesity presents unique clinical challenges in the management of acute pulmonary embolism (PE), requiring a tailored approach to both diagnosis and treatment. However, current international guidelines offer limited guidance on specific strategies for managing PE in patients with obesity, often leaving clinicians with uncertainty. The coexistence of obesity and PE complicates diagnostic accuracy due to technical limitations and significantly influences both pharmacologic and interventional treatment decisions. Adding to this complexity is the "obesity paradox," whereby overweight and obese patients may exhibit better survival outcomes than those of normal weight, a phenomenon that complicates the understanding of PE pathophysiology and may contribute to the under-recognition of key risk factors for acute PE. This comprehensive overview offers a comprehensive analysis of the intricate relationship between obesity and PE, emphasizing pathophysiological mechanisms, clinical implications, diagnostic challenges, and evidence-based management approaches. (JACC. 2025;86:1885-1899) © 2025 by the American College of Cardiology Foundation.

Obesity has emerged as a significant global health issue, with the World Health Organization reporting that approximately 890 million adults aged ≥18 years are classified as obese.[1,2] This chronic condition, frequently observed in clinical care, has reached epidemic levels in both Europe and the United States,[3] contributing to a higher incidence of various chronic diseases, especially cardiovascular diseases (CVDs), which are associated with elevated mortality rates worldwide.[4] The increasing prevalence of obesity is primarily attributed to a chronic imbalance between caloric intake and expenditure, typically identified by a body mass index (BMI) of ≥30 kg/m^2.[5] Additionally, the distribution of body fat is crucial for health outcomes. Visceral adipose tissue (VAT), which accumulates around internal organs, is particularly concerning due to its metabolic activity and strong

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index
BNP = brain natriuretic peptide
CDTs = catheter-directed treatments
CT = computed tomography
CTPA = computed tomography pulmonary angiography
CTEPH = chronic thromboembolic pulmonary hypertension
CV = cardiovascular
CVDs = cardiovascular diseases
DOAC = direct oral anticoagulant
DVT = deep vein thrombosis
EAT = epicardial adipose tissue
GLP1 = glucagon-like peptide-1
IVC = inferior vena cava
LMWH = low-molecular weight heparin
NT-proBNP = N-terminal pro-brain natriuretic peptide
PE = pulmonary embolism
PESI = pulmonary embolism severity index
RCT = randomized controlled trial
RRCT = registry-based randomized controlled trials
RV = right ventricle
sPESI = Simplified Pulmonary embolism severity index
UFH = unfractionated heparin
VAT = visceral adipose tissue
VTE = venous thromboembolism

association with increased overall and cardiovascular (CV) mortality.[6] Beyond its established links to CVDs and diabetes,[7] obesity is recognized as an independent risk factor for venous thromboembolism (VTE), in particular, pulmonary embolism (PE).[8,9] Understanding the complex interplay between obesity and PE is crucial for effective clinical management. Obese individuals often encounter unique diagnostic and therapeutic challenges that can complicate their management.

This state-of-the-art review provides a comprehensive overview of the complex relationship between obesity and PE, focusing on the underlying mechanisms, clinical implications, diagnostic challenges, and management strategies. We specifically chose to focus on PE rather than including deep vein thrombosis (DVT), a potential precursor of PE or the broader spectrum of VTE, because PE poses unique diagnostic and therapeutic challenges, especially in the light of the widespread use of catheter-directed treatments (CDTs) in patients with obesity and an immediate clinical threat with a consequent PE-specific public health burden.

METHODOLOGY

In the present review, international guidelines and investigations, in the English language, were primarily selected based on consensus between the coauthors. A search of PubMed was performed to ensure that no potentially relevant studies or consensus documents were missed (“Pulmonary Embolism” [MAJR] OR pulmonary*[TI] AND [embolism*(TI) OR thromboembo*(TI)] AND obesity* [TI], date last searched: May 28, 2025). Differences and disagreements in opinion, if any, were addressed through meetings and electronic communications. Areas of uncertainty were also noted with the hopes that future basic and clinical research will advance knowledge in this field.

EPIDEMIOLOGIC EVIDENCE LINKING OBESITY TO PE

Numerous epidemiologic studies have consistently highlighted a strong relationship between obesity and an increased risk of PE occurrence.[8,9] Meta-analyses and large cohort studies have demonstrated a direct, linear relationship between increasing BMI and a higher risk of PE.[10-12] Although the exact magnitude of this association can vary, evidence suggests that obese individuals face a 2- to 3-fold higher risk of developing PE compared with individuals of normal weight (BMI: 18.5-24.9 kg/m^2).[10-12] Furthermore, a consistent body of literature has shown that patients classified as obese exhibit lower early- and intermediate-term mortality after PE compared with nonobese patients, revealing a relationship also seen in other CVDs.[5,9,13]

VISCERAL OBESITY. The relationship between VAT and acute PE remains a topic of debate, with studies offering conflicting results. Although visceral adiposity has been implicated in thrombotic risk through mechanisms, such as chronic inflammation, endothelial dysfunction, and altered fibrinolysis (eg, elevated plasminogen activator inhibitor-1 levels from VAT),[14] its association with mortality in PE patients remains unclear. For instance, a retrospective analysis of 1,974 gastrointestinal cancer patients demonstrated that VAT volume, but not BMI or subcutaneous fat, was independently associated with the risk of incidental PE, with an OR of 1.96 (95% CI: 1.25-3.06).[14] However, evidence on the prognostic role of VAT in acute PE has yielded mixed and conflicting results regarding its association with mortality.[15] After 30 days from acute PE, surviving patients had a significantly higher mean epicardial adipose tissue volume (EAT) compared with nonsurvivors (154.6 ± 84.5 cm^3 vs 128.3 ± 65.0 cm^3; $P = 0.02$), but similar EAT density (−76.0 ± 8.4 HU vs −79.4 ± 8.3 HU; $P = 0.89$). In univariate logistic regression analysis, higher EAT density (per SD increase) was significantly associated with 30-day mortality (OR: 1.06; 95% CI: 1.01-1.08; $P < 0.001$), whereas EAT volume was not independently associated with mortality after adjustment for simplified pulmonary embolism severity index (sPESI) score (OR: 1.0; 95% CI: 1.0-1.0; $P = 0.38$).[16] These findings, derived from small observational studies, may lack statistical power, underscoring the need for larger, well-designed trials to determine whether VAT measures should inform risk stratification and treatment planning in PE.[17,18]

OBESITY PARADOX. The so-called “obesity paradox” in PE describes the somewhat counterintuitive observation that, although obesity is a well-established and known risk factor for PE, patients with obesity often experienced better in-hospital survival than their normal-weight counterparts[19-24] (**Table 1**). This phenomenon has been documented in several studies, even after adjusting for factors like age, sex, comorbidities, and use of reperfusion

TABLE 1 Studies Demonstrating the Obesity Paradox in the Short-Term Period Among Obese Patients With Acute PE

Author	Dataset	Period of Enrollment	Definition of Obesity	Adjusted Risk for 30-d or In-Hospital Mortality
Stein et al[20]	National inpatient sample	1998-2008	ICD-10 codes	RR (obese vs nonobese): 0.58[a]
Alkhalfan et al[21]	Single-center	2020-2023	Nonobese: BMI 18.5-29.9 kg/m^2 Obese: BMI ≥30 kg/m^2	HR (obese vs nonobese): 0.29 (95% CI: 0.09-0.92)[b]
Garg et al[19]	National inpatient sample	2016-2020	Nonobese: BMI <30 kg/m^2 Obese: BMI ≥30 kg/m^2	OR (obese vs nonobese): 0.63 (95% CI: 0.60-0.65)
Shachar et al[22]	National inpatient sample (high-risk patients)	2016-2019	Nonobese: <30 kg/m^2 Obese: BMI ≤30 to <40 kg/m^2 Severely obese: BMI ≥40 kg/m^2	OR obese vs nonobese: OR: 0.50 (95% CI: 0.46-0.55) Severely obese vs nonobese: OR: 0.69 (95% CI: 0.64-0.74)
Chopard et al[23]	Burgundy Franche-Comté FRANCE registry	2011-2021	Nonobese: BMI <30 kg/m^2 Obese: BMI ≥30 kg/m^2	Obese vs nonobese: HR: 0.61 (95% CI: 0.45-0.83)
Barba et al[24]	RIETE registry	Up to March 2007	Underweight: <18.5 kg/m^2 Normal weight: BMI ≤18.5 to ≤24.9 kg/m^2 Overweight: BMI ≤25.0 to <30.0 kg/m^2 Obese: BMI ≥30 kg/m^2	Obese vs nonobese: OR: 0.6 (95% CI: 0.4-0.8)[a]

[a] CI not reported. [b] Refers to PE-related mortality.

BMI = body mass index; PE = pulmonary embolism; RR = relative risk.

therapies. Notably, those with obesity class I (BMI: 30-34.9 kg/m^2) and II (BMI: 35-39.9 kg/m^2) appear to gain the greatest advantage. Conversely, underweight patients are typically associated with higher mortality risk.[19,25] Several hypotheses aim to explain this unexpected finding. One suggests that metabolically healthy obese individuals, a growing segment of the population, may possess a better metabolic reserve or be less affected by disease-associated weight loss, leading to better outcomes.[26] Another explanation is something called “collider stratification bias,” a statistical phenomenon that can create spurious associations, making a harmful exposure like obesity appear protective due to imbalances in unmeasured factors like smoking,[27] which is a risk factor for PE but is also associated with lower body weight.[19] Additionally, low body weight has been associated with increased mortality in patients with PE. Several studies, including large registry data, have demonstrated that underweight individuals with PE tend to have worse clinical outcomes compared with their overweight or mildly obese counterparts.[19] This is often attributed to higher rates of active cancer, poor physiological reserve, and frailty in low-BMI patients.[28,29]

Patients with obesity may be more often treated with systemic thrombolysis and surgical embolectomy than lean counterparts of concern over frailty.[25] The relationship between obesity and bleeding risk during thrombolytic therapy for PE is complex. Previous investigations suggest that obese patients may have a lower risk of major bleeding compared with their nonobese counterparts when treated with systemic thrombolysis.[30] One proposed explanation lies in the altered pharmacokinetics observed in obesity, including increased volume of distribution and faster drug clearance, which may reduce peak plasma concentrations of thrombolytic agents and limit their bleeding potential.[22] Additionally, adipose tissue may serve as a reservoir, sequestering a portion of the circulating drug and thereby blunting its systemic fibrinolytic effects.[22] Nonetheless, the validity and implications of the obesity paradox remain a subject of debate. Current research may be limited by underestimation of PE incidence, lack of detailed data on PE severity and cause of death, and potential residual confounding, factors that complicate our understanding of PE pathophysiology.[31]

RISK AND FACTORS LINKING OBESITY AND ACUTE PE

Obesity augments the risk of acute PE through multifactorial pathways (Figure 1).

PROTHROMBOTIC STATE. Obesity has been shown to contribute to a prothrombotic state marked by elevated fibrinogen, factor VII/VIII, and von Willebrand factor, increased platelet activity and aggregation,[32] and reduced endogenous anticoagulants.[33,34] Visceral adiposity further impairs fibrinolysis via increased plasminogen activator inhibitor-1.[12] Furthermore, insulin resistance and dyslipidemia disrupt endothelial homeostasis, reducing nitric oxide bioavailability and promoting adhesion molecule expression, which may trigger endothelial dysfunction and facilitate thrombus formation.[35,36]

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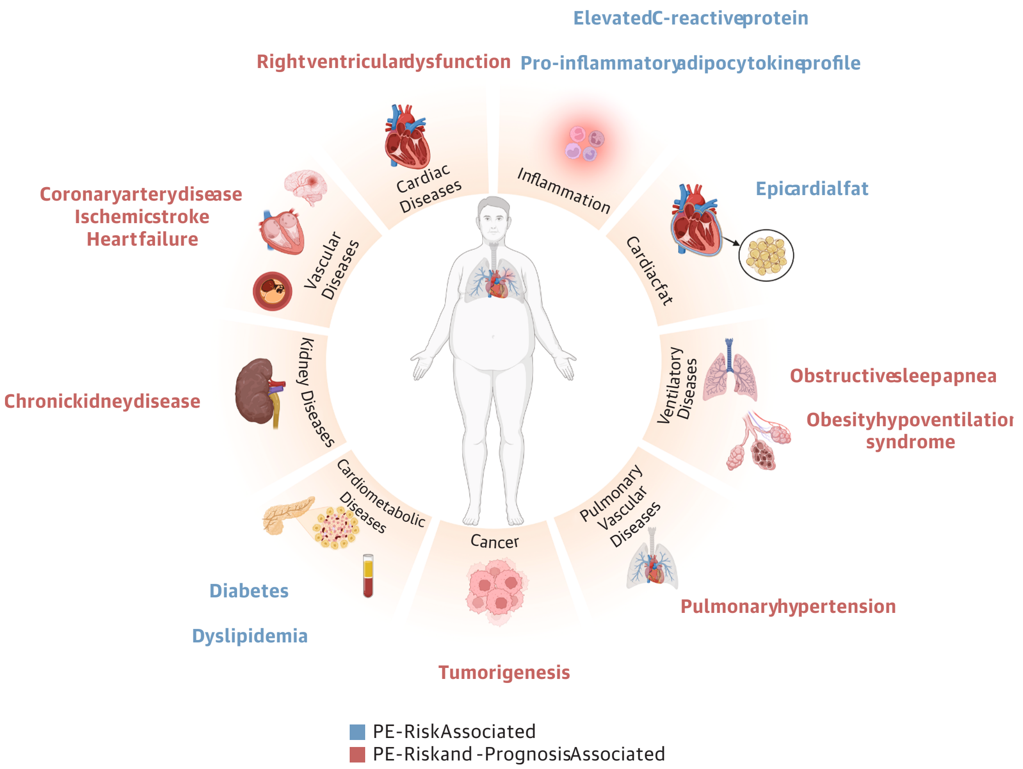
FIGURE 1 **Systemic Effects of Obesity Influencing the Risk and the Prognosis of Patients With Acute PE**


Elevated C-reactive protein
Right ventricular dysfunction
Pro-inflammatory adipocytokine profile
Cardiac Diseases
Inflammation
Coronary artery disease
Ischemic stroke
Heart failure
Vascular Diseases
Epicardial fat
Cardiac fat
Kidney Diseases
Chronic kidney disease
Ventilatory Diseases
Obstructive sleep apnea
Obesity hypoventilation syndrome
Cardiometabolic Diseases
Cancer
Pulmonary Vascular Diseases
Diabetes
Dyslipidemia
Pulmonary hypertension
Tumorigenesis
🟦 PE-Risk Associated
🟥 PE-Risk and -Prognosis Associated

Original image created using Biorender. PE = pulmonary embolism.

Moreover, increased intra-abdominal pressure and compression of the iliac veins impair venous return and promote venous stasis, a condition further exacerbated by the sedentary lifestyle commonly associated with obesity, increasing the risk of VTE by approximatively 20%.[33,37,38] Additionally, adipose tissue releases proinflammatory cytokines, including interleukin-6 and tumor necrosis factor alpha, which activate coagulation cascades and platelet aggregation.[33]

OBESITY-DRIVEN COMORBIDITIES. Obesity amplifies PE risk also indirectly of its association with comorbidities, like coronary artery disease, diabetes, heart failure, obesity hypoventilation, cardiometabolic risk, obstructive sleep apnea, type 2 diabetes mellitus, arterial hypertension, and cancer, which independently predispose to acute PE.[39-45] In fact, the metabolic syndrome and its component criterion, abdominal adiposity, were independently associated with a 91% and 66% relative increase in the odds of VTE, respectively, after adjustment for age, sex, and obesity.[46] Obesity-related obstructive sleep apnea exacerbates hypoxia-induced pulmonary vasoconstriction, endothelial dysfunction, and platelet activation, independently increasing VTE risk.

CARDIOPULMONARY CONSEQUENCES. Among a cohort of 8,285 patients, increased BMI was associated with worse indices of right ventricular (RV) function, which may impact cardiac reserve[47,48] in the setting of acute PE. Although increased BMI has also been correlated with an increased odd of pulmonary hypertension, obesity is associated with a 23% relative reduction in mortality in the setting of pulmonary hypertension.[49] Such an obesity paradox in patients with pulmonary hypertension harmonizes with that observed in those with PE. A potential explanation could arise from the observation that obesity is associated with larger RV end-diastolic volumes and stroke volume that may be beneficial in settings of RV pressure overload.[50] When considering left-sided changes in cardiac structure, obesity is associated with a left atrial and ventricular dilatation, which are associated with a decreased survival in patients with acute PE.[51,52]

TABLE 2 Common Clinical Challenges and Potential Solutions in the Diagnosis and Risk Stratification of Acute PE in Patients With Obesity

Aspect of Clinical Care	Challenge	Potential Solution
Pretest probability of PE	Symptoms and signs may be missed or misattributed to obesity or its related comorbidities	Increase awareness of obesity as a risk factor for PE through patients and physicians Creation and validation of decision support tools, for the prompt recognition and quantification of pretest probability of PE in patients with obesity and compatible signs and symptoms
D-dimer	Reduced specificity in obesity; elevated baseline due to chronic inflammation	Evaluate the diagnostic accuracy of BMI-adjusted thresholds
BNP	Lower serum levels in obese patients may mask RVD	Use an integrated approach combining serum biomarkers with imaging findings for the assessment of ventricular function Promote research on alternative biomarkers reflecting the ventricular function not influenced by the obese status
Diagnostic imaging - CTPA	Weight limits of CT scanners Need for increased contrast medium Higher radiation exposure Higher likelihood of nondiagnostic or indeterminate studies	Develop access to high-weight-capacity scanners Validate optimal scan settings for CTPA in obese patients
V/Q scanning	Weight limit of the CT table Artifacts due to concomitant pulmonary disease as COPD or restrictive lung diseases	Prefer CTPA in obese patients, if feasible Adjust the radiotracer dose based on BMI to enhance image quality without significantly increasing radiation exposure
Ultrasound (TTE and CUS)	Poor acoustic window for transthoracic due to body habitus echocardiography Limited image quality for deep vein imaging due to body habitus Higher likelihood of nondiagnostic or indeterminate studies	Advanced training for ultrasound in obese patients
Risk stratification	Complex assessment of vital signs due to obesity Technical limitation for the assessment of RVD using either CT scanner or TTE Challenges in distinguishing acutely from chronic RVD dysfunction due to obesity-related comorbidities	Standardization or RVD reporting in obese patients Advanced training of sonographers and physicians in echocardiographic assessment of patients with obesity Comprehensive assessment of parameters of RV size and function to enhance detection of acute-on-chronic changes

Images are obtained from Biorender.

BNP = B-type natriuretic peptide; COPD = chronic obstructive pulmonary disease; CT = computed tomography; CTPA = computed tomography pulmonary angiography; CUS = compression ultrasound; RV = right ventricular; RVD = right ventricular dysfunction; TTE = transthoracic echocardiography; V/Q = ventilation/perfusion; other abbreviations as in Table 1.

DIAGNOSTIC CHALLENGES IN PATIENTS WITH OBESITY AND SUSPECTED PE

DIAGNOSIS. Diagnosing and risk-stratifying acute PE in patients with obesity presents unique challenges due to limitations in imaging, biomarker reliability, and gaps in risk-assessment algorithms (Table 2). Obesity imposes significant technical and diagnostic challenges across imaging modalities used to diagnose PE. Increased body habitus often obscures anatomical landmarks, complicating patient positioning and procedural accuracy.[53] Computed tomography pulmonary angiography (CTPA) currently represents the gold standard technique for the diagnosis of acute PE.[54] However, obesity is associated with a higher likelihood of nondiagnostic or indeterminate CTPA studies, potentially due to impaired vascular opacification and motion artifacts.[53] Obesity can interfere with the performance of CTPA due to weight limit of the table, inability to physically fit the patient into the scanner, and poor image quality.[55] In addition, imaging in patients with obesity typically necessitates higher radiation doses and prolonged acquisition times, cumulatively elevating radiation exposure.[56] Given the expanded circulating blood volume in this population, administration of greater volumes or higher concentrations of contrast medium is often required to achieve optimal vascular enhancement.[57,58] Emerging technologies such as dual-energy computed tomography (CT) may improve PE detection through material decomposition imaging and perfusion mapping. Nevertheless, early-generation CT systems are constrained by a reduced field of view, posing challenges for imaging larger patients.[59] Although CT venography is rarely performed as a stand-alone study, it retains utility in evaluating deep venous structures such as the calf veins, iliac veins, inferior vena cava (IVC), and profunda femoris veins, particularly in patients with obesity with suspected DVT. The use of ventilation-perfusion scanning also has some intrinsic limitations in such patients with acute PE,[55] apart from table weight limits and degradation of image quality. The presence of coexisting lung disease, as chronic obstructive pulmonary disease, which is a common comorbidity in subjects with obesity,[60] may complicate the diagnosis. Indeed, pulmonary perfusion abnormalities are prevalent in patients with chronic obstructive pulmonary disease, but they are potentially reversible.[61,62] Transthoracic echocardiography, routinely used for the risk assessment in acute PE, in patients with obesity is often limited by poor acoustic windows caused by increased body habitus.[63,64] The assessment of chamber sizes and pulmonary arterial pressures in this population must be approached with caution, as ventricular remodeling and pulmonary artery dilatation associated with higher BMI can lead to potential misinterpretation of findings.[55,65] In addition, the use of weight-based indexing methods for chamber size estimation, left ventricular diastolic function, and quantification of valvular hemodynamic may result in misclassification and misleading conclusions.[66] Furthermore, the assessment of pericardial effusion, which has been shown to be a prognostic factor for 30-day mortality in patients with acute PE, can be underestimated due to the poorer acoustic window and/or the presence of epicardial adipose tissue.[15,67] In addition, cardiac output, although difficult to assess using echocardiography, is often higher in obesity, due to increased circulating blood volume and metabolic habitus, possibly implicating risk stratification.

BIOMARKERS. The reliability of biomarkers used in the diagnosis of acute PE or evaluation of RV strain could be biased in patients with obesity. D-dimer sensitivity decreases in obesity, potentially due to hemodilution or chronic inflammation. D-dimer levels are often elevated in patients with obesity, with studies demonstrating a positive correlation between D-dimer concentrations and both waist circumference and BMI.[68] However, the age-adjusted D-dimer cut-off safely rules out PE in obese patients without imaging, increasing diagnostic efficiency from 28% to 38%.[11,62] Additionally, obesity may lower N-terminal pro-brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP) levels due to reduced myocardial stretch or increased clearance, potentially underestimating RV strain.[69] Potential falsely low results of BNP can be found in at least 20% of obese heart failure subjects[70] and lowering the established cut-off concentrations by up to 50% in patients with obesity is reasonable.[71] Furthermore, it was demonstrated that the differences ascribed to obesity are in part explained by sex differences: men have lower NT-proBNP levels than women, but weigh much more.[72] Indeed, in a retrospective analysis of patients with acute PE with extreme obesity, defined as having a BMI $\geq$40 kg/m^2, BNP $<$100 pg/mL was recorded in 20% of patients.[73] However, studies show NT-proBNP levels paradoxically increase with BMI, correlating with RV dysfunction (eg, OR of 2.9 for NT-proBNP $>$600 pg·mL^{-1} in patients having a BMI $\geq$40 kg/m^2).[70,74]

RISK STRATIFICATION. Risk stratification in acute PE is crucial for determining the appropriate treatment and predicting outcomes. About 30% of patients can be treated at home. On the other hand, about 5% to 10% should undergo immediate reperfusion. It should be noted that current prognostic tools, such as the pulmonary embolism severity index (PESI)[75] or its simplified version (sPESI)[76] have not been validated on obese patients and do not incorporate BMI, limiting the prognostic stratification of these patients in daily clinical practice. Tachypnoea may be due to obesity; therefore, the preferred clinical assessment scale seems to be sPESI.[76] Although the BOVA score[77] is a well-validated risk stratification tool designed to predict 30-day PE-related complications in the general population, its application in patients with obesity has not been specifically validated. Furthermore, obesity may influence several BOVA components, such as the interpretation of right ventricular dysfunction (due to suboptimal echocardiographic windows) or the release kinetics of cardiac biomarkers, potentially affecting risk classification. Further studies are warranted to assess its calibration and predictive performance in this specific subpopulation. In these patients there are, as described earlier in this article, difficulties with the interpretation of additional imaging and biochemical tests, which make risk stratification particularly difficult. To date, there are no prospective studies evaluating risk stratification in obese individuals.

DEEP VEIN THROMBOSIS. The concomitant diagnosis of DVT in patients with obesity with acute PE poses challenges due to technical and pathophysiological limitations. The increased adipose tissue may complicate the performance and interpretation of compression ultrasonography, which remains the first-line diagnostic tool to confirm the presence of a thrombosis below the infrainguinal ligament, leading to overdiagnosis.[53] Furthermore, the image quality of Doppler ultrasound can be inadequate to assess the patency of the iliac veins and IVC. The fact that typical clinical signs of DVT, such as swelling, may be less evidence and masked by comorbidities adds additional complexity.[78] It must be noted that the use of computed tomography angiography to confirm or exclude DVT has not fully validated and artefactual findings also due to low-flow situations or poor respiratory compliance cannot be excluded. Isolated DVT is more frequent on the left side due to venous compression of the common iliac vein by the right common iliac artery (May-Thurner anatomy). However, according to a Dutch study from 2010, patients with obesity are not subject to a higher risk of isolated left-sided DVT.[79] This means that obesity does not lead to worsening of iliac compression, and, therefore, the potential for embolization is not reduced as it appears to be among patients with May-Thurner syndrome. In terms of management, the treatment of DVT in patients with obesity generally follows standard anticoagulation protocols. However, as with PE, dose adjustment and careful monitoring may be necessary to ensure therapeutic efficacy, particularly when using weight-based low-molecular weight heparin (LMWH) or unfractionated heparin (UFH). Direct oral anticoagulants (DOACs) have shown efficacy and safety in patients with obesity, although caution is advised in those with a BMI >40 kg/m^2 or weight >120 kg, pending further confirmatory studies.[80] In such patients, standard doses of rivaroxaban or apixaban seem to be appropriate regardless of elevated BMI or body weight, although no clinical data are currently available for edoxaban or dabigatran in this specific population.[80]

TREATMENT STRATEGIES FOR PE IN PATIENTS WITH OBESITY

In the setting of acute PE, obesity introduces several important clinical challenges that must be carefully considered in both treatment and prevention (**Table 3**). Patients with obesity, particularly those who are hemodynamically unstable (eg, high-risk PE), often present difficulties in initial management, including imaging limitations, vascular access, and procedural interventions such as thrombolysis or catheter-based therapies. Anticoagulation remains the cornerstone of PE treatment, but in obese individuals accurate weight-based dosing is essential to achieve and maintain therapeutic levels, particularly when using UFH or LMWH. Moreover, altered pharmacokinetics and concerns regarding drug absorption may complicate the use of DOACs. Prevention is also more complex in this population due to increased baseline thrombotic risk, reduced mobility, and variable responses to standard prophylactic regimens. These multifactorial issues underscore the need for individualized treatment strategies and further research to optimize care in this growing patient population[81] (**Central Illustration**).

SYSTEMIC FIBRINOLYSIS AND CDTs. For patients presenting with hemodynamic instability, systemic fibrinolysis may be indicated but must be approached cautiously due to potential existence of relative and/or absolute contraindications due to the high burden of comorbidities in these patients. Current evidence suggests that systemic fibrinolysis at conventional doses has similar efficacy and bleeding rates in patients with morbid obesity compared with those who do not have increased BMI.[30] CDT has recently emerged as a promising option for treating PE in hemodynamically unstable patients and probably in selected hemodynamically stable patients with PE, experiencing sudden hemodynamic deterioration, normotensive shock, or not showing any clinical improvement using standard anticoagulation.[82] In this regard, there are limited data regarding the safety and efficacy of CDTs in patients with obesity. However, available evidence seems to show that CDTs can be performed safely with a high procedural success rate and low complication incidence.[83] Moreover, technical challenges, such as the visualization of the target area, the availability of appropriately sized transcatheter equipment, and the requirement for higher doses of radiation, pose significant limitations.

Obesity also presents unique challenges in vascular access, particularly when using the femoral route for CDTs. Evidence suggests that higher BMI is associated with an increased risk of low femoral artery puncture, which can lead to vascular complications, especially when large-bore access is required[84] as in the case of some CDT devices. When local lysis is preferred, particularly with low-dose regimens with or without ultrasound facilitation, alternative access sites should be considered. The internal jugular and basilic veins offer safer routes, especially given that the required catheter sizes are relatively small, typically 5-F for standard lysis catheters and 6-F for EKOS Endovascular System catheters, minimizing vascular trauma and improving procedural safety in patients with obesity.[82] Last, obtaining venous femoral access and achieving hemostasis in patients with obesity tend to be more challenging compared with their nonobese counterparts. The anticoagulation regimen in the perioperative period of CDT typically relies on intravenous UFH. During mechanical thrombectomy, an activated clotting time of 150 to 200 s is generally targeted, with the UFH dose adjusted according to body weight and any baseline anticoagulation therapy. However, the optimal dosing of UFH during local thrombolytic treatment remains poorly defined. It has been proposed to administer UFH at 500 to 1,000 IU/h,

TABLE 3 Common Clinical Challenges and Potential Solutions for the Treatment and Prevention of Acute PE in Patients With Obesity

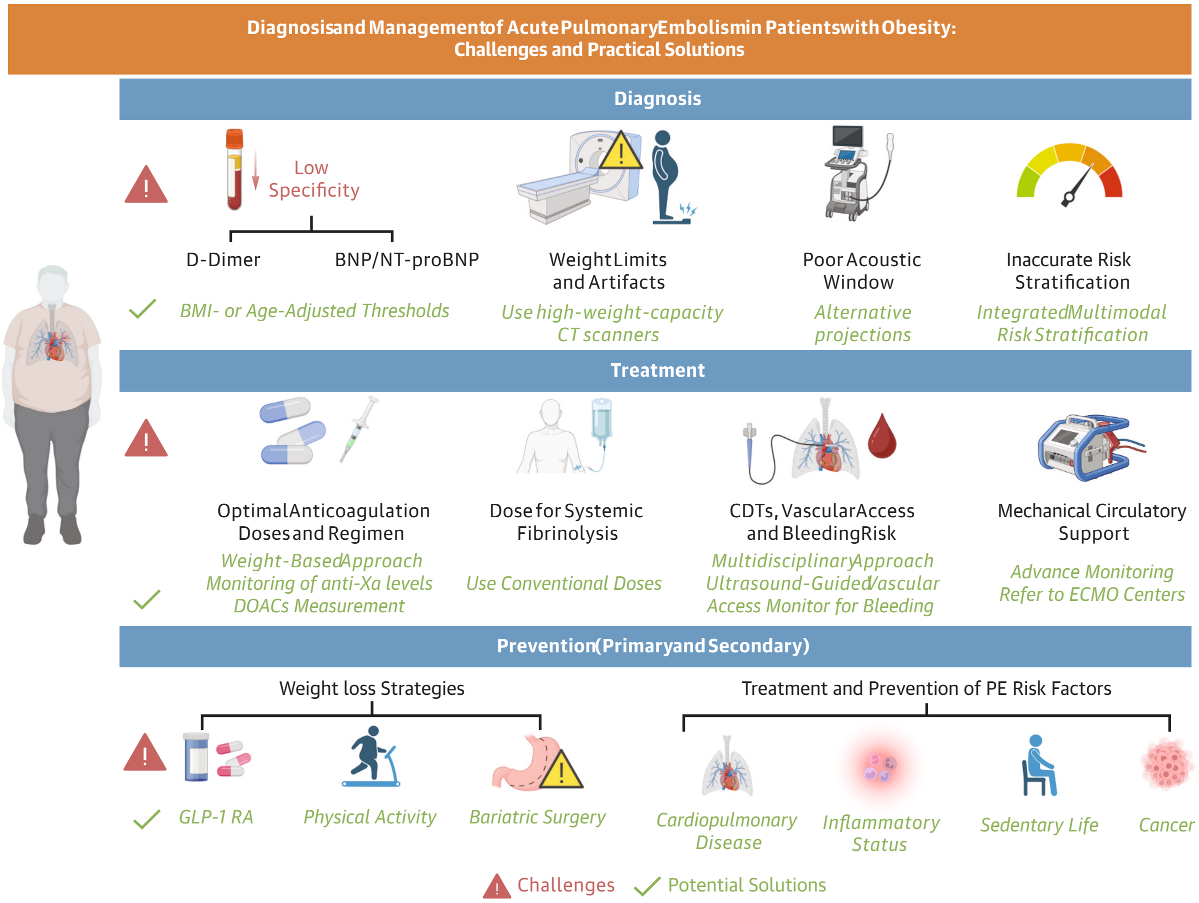
Aspect of Clinical Care	Challenge	Guidance	Potential Solution
Anticoagulation management	Challenges in administering UFH or LWMH Difficulties and delays in achieving adequate anticoagulation using UFH Challenges of monitoring aPTT or anti-Xa levels Limited data on the efficacy of DOACs in patients with BMI extremes Absence of an established therapeutic range for anti-Xa levels Challenges in achieving and maintaining therapeutic levels of VKA	For LMWH: dose using actual body weight; monitor anti-Xa levels in BMI $>$40 kg/m^2 or $>$150 kg, aiming for standard therapeutic range For Fondaparinux the treatment dose should be increased to 10 mg once daily in patients weighing $>$100 kg For UFH: use weight-based nomograms and frequent aPTT/anti-Xa monitoring For DOACs: monitor drug levels if available or consider warfarin or LMWH in BMI extremes	Follow dosing protocols also with pharmacy guidance for appropriate parenteral and oral anticoagulant dosing Preferred use of LMWH when appropriate to ensure adequate therapeutic anticoagulation Emphasis on shared decision-making with the patient and provider to acknowledge recurrence and bleeding risks, lifestyle implications, cost, and preferences
Reperfusion therapy	Limited data and experience with reperfusion therapies for obese subjects Concerns about excess bleeding risk Challenges of vascular access for catheter-based intervention Higher doses of radiation compared with nonobese patients using CDTs Technical and surgical limitations for surgical embolectomy	Add obesity as an indication for PERT consultation in intermediate- to high-risk and high-risk patients Prefer less invasive interventions when feasible If surgical embolectomy is indicated, ensure technical feasibility and surgical expertise	Encourage inclusion of obese patients in RCTs to enhance data on efficacy and safety Implementation of PE response teams to aid in selection of reperfusion therapy in absence of obesity-specific guidelines Collect prospective data to inform practice
Management of hemodynamic instability	Lack of obesity-specific data for hemodynamic support in patients with obesity Limited data focused on the use of ECMO and RV mechanical circulatory support in high BMI Difficult assessment of volume status in patients with obesity	Use bedside echocardiography and focused assessment for volume status Promote hub and spoke network with high-volume ECMO centers familiar with obesity	Promote advanced research on hemodynamic instability in obese patients with PE Implementation of PE response teams with critical care expertise to aid in hemodynamic support in patients with obesity
Bleeding risk evaluation	Challenges in the detection of active bleedings, especially access-related, in patients with obesity	Use ultrasound-guided vascular access	Increase awareness and develop obesity-specific protocols
Recognition of VTE recurrence risk	Obesity-related risks are often underappreciated	Consider extended anticoagulation for high-risk obese patients, after assessing bleeding risk Emphasize thromboprophylaxis around high-risk situations like trauma, surgery, and immobility to prevent recurrent events	Increase awareness of obesity and related comorbidities as a risk factor for VTE recurrence through patient and provider education
Lifestyle modification to reduce recurrence risk and overall CV health	Difficulty achieving healthy BMI and reducing obesity-related comorbidities to mitigate risk of de novo or recurrent VTE episodes	Consider GLP-1 RA and bariatric surgery per guidelines Encourage sustained physical activity and diet in all patients	Recognize obesity as a potential modifiable risk factor for VTE Referral to weight management subspecialty clinics Consider medical weight loss therapy, including GLP-1 receptor agonists, and, when appropriate, bariatric surgery Promote regular physical activity and diet Promote research focusing on the impact of lifestyle modification and obesity treatment for the prevention of acute PE

aPTT = activated partial thromboplastin time; CDT = catheter-directed treatment; CV = cardiovascular; DOAC = direct oral anticoagulants; ECMO = extracorporeal membrane oxygenation; GLP-1 = glucagon-like peptide-1; LMWH = low-molecular weight heparin; PERT = pulmonary embolism response team; RA = receptor agonist; RCT = randomized controlled trial; UFH = unfractionated heparin; VKA = Vitamin K antagonist; VTE = venous thromboembolism; other abbreviations as in Tables 1 and 2.

irrespective of body weight, but tailored based on prior use of UFH or LMWH.[85] Notably, obese patients are often under-represented in clinical trials, and, as a result, current recommendations are largely extrapolated from data derived from nonobese populations. This limits the generalizability of existing evidence and may affect the precision of anticoagulation strategies in obese individuals undergoing CDT.

ANTICOAGULATION. Obesity introduces further complexities in the pharmacologic management of acute PE due to altered pharmacokinetic and pharmacodynamic factors, as well as metabolic changes and obesity-related comorbidities. From a pharmacologic perspective, the most significantly impacted parameters are the volume of distribution and drug clearance.[86] A significant number of patients with obesity treated with UFH experienced delays of more

CENTRAL ILLUSTRATION Diagnosis and Management of Acute PE in Patients With Obesity: Challenges and Practical Solutions


Diagnosis and Management of Acute Pulmonary Embolism in Patients with Obesity:
Challenges and Practical Solutions
Diagnosis
Low Specificity
D-Dimer
BNP/NT-proBNP
Weight Limits and Artifacts
Poor Acoustic Window
Inaccurate Risk Stratification
BMI- or Age-Adjusted Thresholds
Use high-weight-capacity CT scanners
Alternative projections
Integrated Multimodal Risk Stratification
Treatment
Optimal Anticoagulation Doses and Regimen
Dose for Systemic Fibrinolysis
CDTs, Vascular Access and Bleeding Risk
Mechanical Circulatory Support
Weight-Based Approach
Monitoring of anti-Xa levels
DOACs Measurement
Use Conventional Doses
Multidisciplinary Approach
Ultrasound-Guided Vascular Access Monitor for Bleeding
Advance Monitoring
Refer to ECMO Centers
Prevention (Primary and Secondary)
Weight loss Strategies
Treatment and Prevention of PE Risk Factors
GLP-1 RA
Physical Activity
Bariatric Surgery
Cardiopulmonary Disease
Inflammatory Status
Sedentary Life
Cancer
Challenges
Potential Solutions

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BMI = body mass index; BNP = brain natriuretic peptide; CDTs = catheter-directed treatments; CT = computed tomography; DOAC = direct oral anticoagulant; ECMO = extracorporeal membrane oxygenation; GLP1-RA = glucagon-like peptide-1 receptor agonists; NT-proBNP = N-terminal pro-brain natriuretic peptide; PE = pulmonary embolism. Original image created using Biorender.

than 24 hours in achieving adequate anticoagulation.[87] Furthermore, most of these patients received either an insufficient heparin bolus, an inadequate initial continuous infusion, or both, in accordance with current dosing guidelines.[87,88] In patients with obesity, achieving therapeutic anticoagulation using UFH may require higher initial doses, although caution is needed to avoid supratherapeutic levels and bleeding.[89] LMWH, such as enoxaparin, are often preferred due to their predictable pharmacokinetics. Standard dosing (eg, 1 mg/kg administered twice daily) based on actual body weight is generally safe up to weights of 150 to 165 kg.[90] However, in patients with severe or morbid obesity, there is emerging evidence that dose capping or dose reduction to 75% to 80% of total body weight may reduce bleeding risk without compromising efficacy.[91,92] If fondaparinux is used, the treatment dose should be increased to 10 mg once daily in patients weighing >100 kg.[91,92]

Although BMI and weight were not exclusion criteria in any of the DOAC registration trials, international guidelines suggest exercising caution or avoiding prescribing DOACs for patients with a BMI >40 kg/m² or a weight >120 kg.[80,93,94] The International Society on Thrombosis and Haemostasis and the European Society of Cardiology guidelines recommend measuring anti-Xa activity in patients with morbid obesity who are prescribed DOACs.[80] However, this approach is problematic because no established therapeutic range for anti-Xa levels exists, leaving clinicians without clear benchmarks for assessing efficacy or safety.[38] This hesitancy persists despite evidence from at least 1 meta-analysis, which found no reduction in efficacy when comparing DOAC use in obese vs nonobese patients within the registration trials.[95] As a result, warfarin is often chosen as the anticoagulant for morbidly obese patients, despite its well-documented challenges in achieving and maintaining therapeutic levels due to frequent dose adjustments and monitoring.[54] For cases in which anticoagulation is contraindicated or recurrent PE occurs despite treatment, IVC filter placement may be considered; however, clinicians must weigh long-term benefits against potential risks and prioritize retrieval as soon as anticoagulation has been safely instituted.[38] In obese patients, filter placement may be technically challenging and is associated with procedural risks, including filter misplacement and increased risk of filter-related thrombosis.[96] Furthermore, placement of an IVC filter generally requires a caval diameter <2.8 cm, which may be exceeded in patients with obesity, potentially limiting eligibility. Recent guidelines emphasize the importance of retrieving temporary filters once the indication has resolved to reduce long-term complications.[97] As such, the role of IVC filters in patients with obesity should be individualized and closely monitored.

Additionally, anticoagulation treatment in patients with acute PE and a previous bariatric surgery presents unique challenges due to altered gastrointestinal anatomy and absorption. Indeed, oral anticoagulants, particularly DOACs, may have variable bioavailability, especially after procedures like Roux-en-Y gastric bypass. Current evidence for the optimal treatment of these patients remains limited, and treatment decisions should be individualized, balancing thrombotic risk, bleeding risk, and potential drug malabsorption.[80,93,94] Importantly, certain types of bariatric surgery, particularly those involving malabsorptive procedures, may alter the pharmacokinetics of DOACs, potentially reducing their bioavailability and anticoagulant effect.

PREVENTION OF PE RECURRENT EVENTS

Reducing BMI and maintaining a healthier weight require significant and sustained commitment from individuals with obesity. Additionally, challenges arise when attempting to balance dietary approaches tailored to various underlying conditions and comorbidities, such as diabetes mellitus, arterial hypertension, dyslipidemia, or end-stage kidney disease. Current international guidelines on the management of acute PE lack dedicated sections addressing lifestyle changes after an acute PE event.[54] In this regard, only the European Society of Cardiology offers general recommendations for cardiovascular risk reduction.[94] Given the availability of novel pharmacologic approaches to lower BMI, future guidelines should also emphasize the importance of lifestyle modifications and pharmacologic treatments in reducing the risk of recurrent PE in patients with obesity. Additionally, regular aerobic exercise, caloric restriction, and balanced diet must be recommended as a primary line for either primary and secondary prevention for PE and more in general CV diseases.[98,99] Addressing obesity through lifestyle changes and/or bariatric surgery after an acute PE may significantly decrease the risk of recurrent VTE and improve overall health outcomes for these individuals.

LONG-TERM PROGNOSIS

Higher BMI has been consistently associated with poorer outcomes of care of patients with acute PE. Mostly, higher BMI has been described to be a relevant determinant of persistent symptoms and quality of life. BMI was reported to be an independent predictor of poorer quality of life as measured with disease-specific and generic quality of life measures, with other predictors involving cardiopulmonary comorbidities, advanced age, and smoking history.[100-103] Obesity proved to be associated with worse physical, mental, as well as social functioning in PE survivors after a follow-up of up to 2 years.[101,102,104] The relevant impact of obesity on physical functioning after PE is exemplified by studies that show that higher BMI predicts poorer results of exercise tests.[103] It was even noted that BMI independently predicted attenuated recovery with less improvement in quality of life, dyspnea scores, and 6-minute walk distance over time.[104] Interestingly, BMI is not associated with persistent perfusion defects after PE,[105] nor with the incidence of chronic thromboembolic pulmonary hypertension (CTEPH), nor health care use or diagnostic delay in the work-up of CTEPH.[105] On the other side, extreme weights seem to be associated with poorer prognosis and recovery after CTEPH surgery, resulting in potentially more frequent selection of obese patients for balloon pulmonary angioplasty.[106]

OBESITY IN ACUTE PE: CLINICAL IMPLICATIONS AND UNMET CLINICAL NEEDS

Reducing the burden of PE in patients with obesity necessitates a comprehensive approach that integrates markers of obesity into risk assessment and management strategies. For example, using advanced imaging techniques, such as dual-energy CT,[107] could improve clot detection in obese patients with a weight of <120 kg, which represents the general limit of the CT tables available on the market, addressing some limitations of traditional methods like CTPA. Similarly, to enhance risk stratification in these subjects, implementing BMI-specific thresholds for NT-proBNP or BNP could help avoid underestimating RV strain in this population. Furthermore, risk models should account for the presence of pulmonary trunk dilation,[108] which is more prevalent in patients with obesity and can significantly impact prognosis. Regarding the anticoagulant treatment, the under-representation of subjects with obesity in previous randomized controlled trials (RCTs) limits the generalizability of findings. Given the higher bleeding risks associated with obesity, especially in patients with a BMI ≥40 kg/m², adjusting anticoagulant dosing based on weight is essential to optimize therapeutic efficacy while minimizing complications. However, due the absence of solid results guiding the anticoagulation strategies in obese patients with acute PE, further RCTs including subgroup analyses based on BMI are necessary to better inform treatment guidelines.

As demonstrated by the STEP (Semaglutide Treatment Effect in People with Obesity)-1[109] and SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Obesity in People with Overweight or Obesity)[110] trials, the advent of glucagon-like peptide-1 (GLP-1) receptor agonists has opened new avenues for managing obesity and its associated CV risks. Moreover, GLP-1 receptor agonists have shown promise in reducing major CV events, including CV death, nonfatal myocardial infarction, and heart failure hospitalization even in diabetic and nondiabetic obese populations.[111,112] However, no data are currently available regarding potential benefits in reducing the risk of recurrent VTE events or reducing CV events in secondary prevention after acute PE. Current large-scale trials on GLP-1 receptor agonists have not prespecified VTE outcomes as primary or secondary endpoints, limiting definitive conclusions regarding their role. Moreover, no publicly registered or widely announced phase 3 trials are currently dedicated to evaluating GLP-1 receptor agonists specifically for secondary VTE prevention. At present, evidence is conflicting. Some data suggest that GLP-1 receptor agonists may increase the risk of DVT, but not PE, with an OR of 1.64 (95% CI: 1.14-2.36), particularly after 1 year of treatment (OR: 2.32; 95% CI: 1.49-3.60).[113] Conversely, other studies indicate that GLP-1 RAs may reduce the risk of VTE overall (HR: 0.79; 95% CI: 0.73-0.83) over a 12-month period, including both acute PE (HR: 0.74; 95% CI: 0.68-0.82) and DVT (HR: 0.81; 95% CI: 0.75-0.88), compared with dipeptidyl peptidase-4 inhibitors.[114] The growing recognition of the potential antithrombotic benefits of GLP-1 receptor agonists, possibly related to attenuation of thromboxane-induced platelet activation, underscores the need for future dedicated clinical trials focused on VTE prevention, particularly in high-risk populations. Incorporating VTE endpoints into upcoming GLP-1 receptor agonists trials, along with mechanistic and real-world studies, will be essential to clarify the role of these agents in VTE management and prevention.

Doubtless, bariatric surgery remains another effective intervention for obesity management, often resulting in greater weight reduction than pharmacologic therapies. Although it is associated with improved CV risk factors and lower mortality rates, further research is needed to understand its impact on specific outcomes related to acute PE. Finally, addressing socioeconomic and racial/ethnic disparities remains another major goal to achieve in the management of obese patients experiencing acute PE. The rising prevalence of obesity is influenced by environmental factors rather than solely genetic or physiological changes.

As of August 3rd, 2025, no registered clinical trial on ClinicalTrials.gov is specifically investigating pharmacologic therapies or anticoagulant dosing strategies exclusively in obese or morbidly obese patients with acute PE. Ongoing trials, such as PEITHO-3 (Pulmonary Embolism International THrOmbolysis Study-3; NCT04430569), are evaluating reduced-dose thrombolysis in intermediate high-risk PE and may include obese patients among other subgroups. However, subgroup analyses in randomized clinical trials often suffer from limited statistical power, which can reduce the reliability of findings and increase the risk of spurious or nongeneralizable conclusions. Given the limitations of traditional RCTs in adequately addressing specific high-risk subgroups like patients with obesity, including challenges in recruitment, ethical concerns, and insufficient statistical power, large prospective observational registries and registry-based randomized controlled trials (RRCTs) may offer a promising alternative. Prospective registries capturing granular, high-quality data on patient characteristics, diagnostic strategies, treatment regimens, and independently adjudicated outcomes can yield valuable real-world insights into the management and prognosis of obese patients with PE. These data sets may also enable better-powered subgroup analyses and propensity-matched comparisons that overcome some of the methodologic limitations of conventional RCTs. Furthermore, RRCTs, conducted within existing clinical registries, combine the internal validity of randomization with the external validity of real-world evidence. They offer efficient trial conduct, broader inclusion criteria, and lower costs, making them particularly well-suited to study under-represented populations, including those with extreme obesity. Future RRCTs could evaluate weight-adjusted anticoagulation strategies, novel risk stratification tools, and safety and efficacy of tailored reperfusion therapies. Harnessing these modern research platforms may help overcome long-standing evidence gaps and support more personalized, effective care for obese patients with acute PE.

Looking ahead, the pharmacologic management of acute PE in obese patients is poised to evolve toward more personalized, safer, and pathophysiologically targeted approaches. One major area of focus will be the optimization of anticoagulant therapy, providing an evidence base for adequate weight-based dosing of LMWH and UFH.[80] Beyond existing agents, novel anticoagulants, such as factor XI/XIa inhibitors, are currently under investigation and may offer comparable efficacy to current therapies with a reduced bleeding profile.[29] Advances in reperfusion therapy, including CDTs and low-dose systemic thrombolysis, are also being refined, with an emphasis on improving safety in obese patients.[30] Hopefully, long-term anticoagulation strategies will likely become increasingly individualized, incorporating risk stratification tools, bleeding scores, and possibly pharmacogenomic profiling to guide duration and intensity of therapy.

CONCLUSIONS

Obesity is a relevant independent risk factor for acute PE, with a complex interplay of pathophysiological mechanisms determining this risk. It is crucial for clinicians to recognize the diagnostic challenges and treatment considerations specific to patients with obesity with suspected or confirmed PE. To effectively address the management of PE in patients with obesity, further research is necessary to refine diagnostic and therapeutic approaches. This includes exploring the long-term effects of weight loss on VTE outcomes and understanding how obesity influences clinical presentation and treatment response. Moreover, the integration of obesity into risk assessment algorithms may be necessary to improve the accuracy of prognostic models and outcomes of care. Finally, weight management strategies are essential in mitigating the risk of recurrent VTE within this population. By focusing on tailored interventions, multidisciplinary collaboration, and ongoing research, health care providers can better navigate the complexities associated with managing acute PE in obese individuals.

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